RESPONSE TO COHEN'S COMMENTS ON THE LUBIN REJOINDER

Dear Editors:

In his recent rebuttal to my paper and its rejoinder (Lubin 1998a; Lubin 1998b), Cohen (Cohen 1999) made several errors of fact and inference, which results in misleading conclusions. Cohen concluded that his ecologic regression provided a good fit to the results of indoor radon studies. However, this conclusion was based on an invalid probabilistic argument. Further, based on both visual and formal statistical evaluations, his model fails to fit indoor radon data, and as such his conclusions are incorrect.

Cohen made factual errors when explaining relative risks (RR) which were markedly discrepant from model predictions. He stated that the Stockholm radon study lacked information on smoking, only 10% of the houses had radon measurements, and he was "unable to relate" a data point. However, investigators had smoking data on nearly all subjects and measured sufficient numbers of houses to cover nearly 80% of the exposure period between 1945 and 5 y prior to the 1983–1985 enrollment period (Pershagen et al. 1992). Cohen's unknown RR has value 1.7 with 95% CI (1.0,2.9) (Table 2 in Pershagen et al. 1992). Cohen also alluded to a "horizontal error bar" in the Missouri study. He implied that the mean did not represent the category-specific radon value. However, a simple inspection shows that his regression line lies entirely outside the 95% confidence interval (CI), regardless of the precise location of the RR.

Cohen suggested that his ecologic model fitted the indoor radon data because "only 2 of 33" of the 95% CIs failed to include his regression line. This is an incorrect probabilistic interpretation of CIs. A 95% CI provides that level of assurance that the true parameter lies *somewhere* within the interval. However, Cohen treated the CIs as if they were independent tests of the null hypothesis. RRs and CIs within each radon study are not independent, but statistically dependent. This is obvious since changing the definition of the baseline (i.e., lowest exposure) category alters all RRs and CIs. In theory one could encompass Cohen's regression line entirely within the CIs by simply defining narrower radon categories and thereby increasing widths of the CIs. Thus, Cohen's "assessment of model fit" is not valid.

Cohen suggested that his model fitted the RRs for individual studies. However, this also is incorrect as a variety of methods shows that his risk model based on descriptive data provides a poor characterization of lung cancer risks in the more analytically sound indoor radon studies. Fig. 1 shows category-specific relative risks (RR) from nine case-control studies (eight studies from a meta-analysis (Lubin and Boice 1997), and the new Cornwall study (Darby et al. 1998), the BEIR VI miner-based extrapolation (National Research Council 1999), and Cohen's linear-quadratic ecologic model. All models are adjusted to pass through 22 Bq m^{-3}, which is used to represent the mean of the lowest concentration category, although mean radon for the lowest category ranged from 22 to 55.5 Bq m^{-3}. It is apparent that visually Cohen's model does not fit the indoor radon data. Cohen's model predicts a protective effect of radon in the range 22 to 291 Bq m^{-3}, while the data show no evidence of a protective effect in this range.

Fig. 2 shows RRs for each indoor radon study, along with three regression lines. The models are as follows: (1) a log-linear model (dotted line): $RR(x) = \exp[\beta(x-x_o)]$, where x is radon concentration, x_o is the mean concentration for the lowest category, and β, the unknown parameter, is estimated within study by weighted least squares regression; (2) Cohen's linear-quadratic ecologic regression model (dashed line); (3) the linear excess RR model (solid line): $RR(x) = 1 + \beta x$, where β is fixed at 0.001107 Bq m^{-3}. This value is derived from the excess RR estimate of 0.0117/Working Level Month and assuming 25 y exposure (National Research Council 1999). This model was used for simplicity, since it closely approximates extrapolations of the BEIR VI model. The pooled model from the meta-analysis was similar to the BEIR VI extrapolation and was omitted. All models were adjusted to pass through the mean radon level of the lowest category in each study. In contrast to Cohen's presentation (Cohen 1999) plots use a common scale to avoid perceptual distortion. Because Cohen's model predicts RRs less than 1 under about 300 Bq m^{-3}, Cohen's model predictions are less disparate for "negative" studies, such as the Winnipeg and Shenyang studies.

A variety of methods can be used to formally compare model fits, and all show a poor fit for Cohen's ecologic model. First, very simply one can count the number of RRs falling below and above the various prediction lines. Within each study, the study-specific log-linear models generally provided good fits to the RRs, and not surprisingly 15 of 28 RRs fell below the prediction lines. Based on a binomial distribution, the p-value of observing this number or a number more extreme is $p = 0.43$. For the miner model, 15 of 29 points fell below the prediction lines with $p = 0.50$. For Cohen's model, 7 of 31 fell below the prediction lines with $p = 0.002$.

Using residual sums of squares, F-statistics were calculated comparing the fit of the indoor polling model, the BEIR VI model, and the Cohen linear-quadratic model to the study-specific log-linear model. The values of the F-statistics are valid comparisons of model fit. However, p-values for the BEIR VI model and Cohen model are only approximate because those models are not nested in the (log-linear) study-specific model, which is only approximately linear. Fig. 3

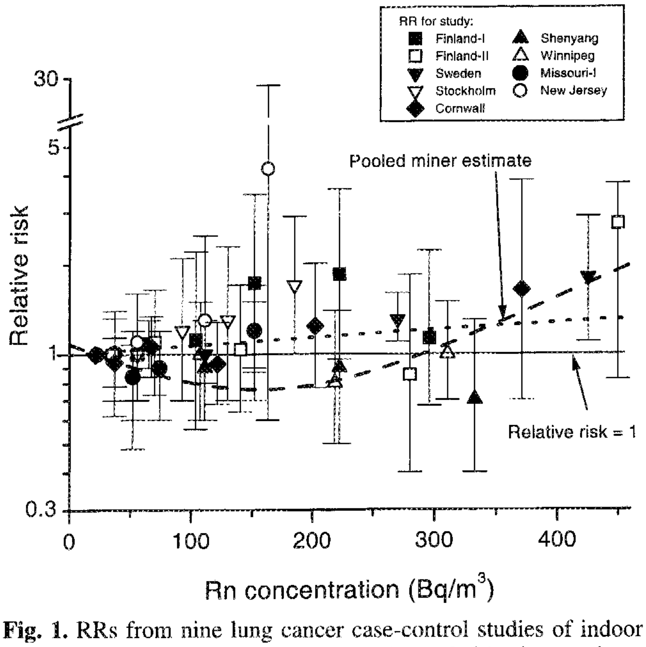

Fig. 1. RRs from nine lung cancer case-control studies of indoor radon. Dotted line depicts extrapolation of RR from miners (National Research Council 1999); dashed line depicts linear-quadratic ecologic regression model (Cohen 1999); and solid line depicts a RR of one.

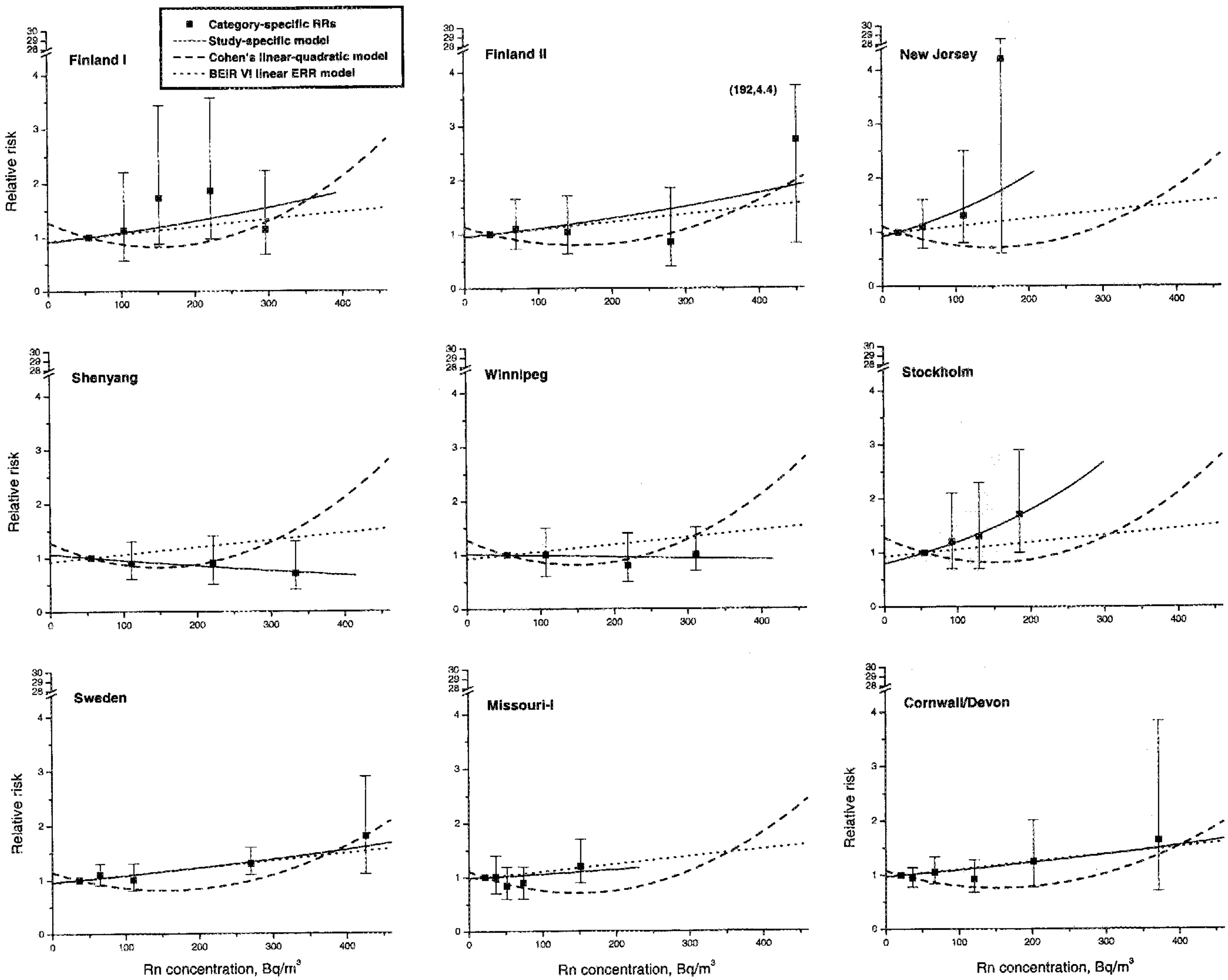

Fig. 2. RRs from nine lung cancer case-control studies of indoor radon. Solid line shows fitted log-linear model to data from each study; dotted line depicts extrapolation of RRs from miners (National Research Council 1999); dashed line depicts linear-quadratic ecologic regression model (Cohen 1999).

shows the F-statistics and 95% and 99% quantiles. In 7 of 9 studies, the F-statistic for the Cohen model exceeds the values for the other models.

The Pearson chi-square goodness-of-fit statistics (sum over a study of the squared difference of the observed and expected RR divided by the expected) showed the same results.

I agree with Cohen's statement that average dose does not determine average risk. However, the logical consequence of this fact is that any functional relationship between average dose and average risk provides no direct information about the relationship between individual dose and individual risk. Proponents of ecologic studies seem not to accept the fact, demonstrated both theoretically (Lubin 1998a) and practically (Lagarde and Pershagen 1999), that bias in ecologic studies can occur due to within-county correlations among risk factors and that the correlations, which may vary across counties, cannot be modeled using only county level data. Even small correlations among risk factors can induce large biases at the county level, which cannot be "adjusted" using area level data, regardless of how finely counties are stratified. Thus, no valid inference can be made from a county-level relationship to individual exposure-response, and conversely, absent information on within-county correlations, no valid inference can be made from the exposure-response for individuals to the county-level. As a result, there is no unambiguous way to test a LNT model for individual radon exposure using only county data. Cohen has attempted to validate his model by suggesting consistency with indoor radon studies. My analyses show clearly that the Cohen model just does not agree with results from the indoor radon studies.

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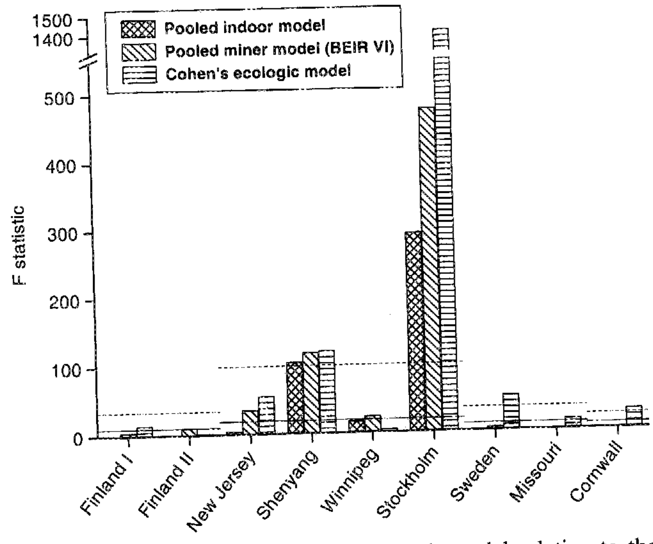

Fig. 3. F-statistics for comparison of each model relative to the study-specific one-parameter, log-linear model. Solid and dashed lines depict 0.05 and 0.01 quantiles of the F-distribution, respectively.

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